



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,385	02/05/2002	John E. Adamou	469290-589	8182

7590 09/19/2005
CARELLA, BYRNE, BAIN, GILFILLAN,
CECCHI, STEWART & OLSTEIN
6 Becker Farm Road
Roseland, NJ 07068

EXAMINER

DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
----------	--------------

1645

DATE MAILED: 09/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/067,385

Applicant(s)

ADAMOU ET AL.

Examiner

S. Devi, Ph.D.

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 July 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4,11-13,18 and 21 ~~is/are~~ are pending in the application.
- 4a) Of the above claim(s) 12 and 13 ~~is/are~~ are withdrawn from consideration.
- 5) ☐ Claim(s) 4 and 18 ~~is/are~~ are allowed.
- 6) ☒ Claim(s) 1,3,11 and 21 ~~is/are~~ are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 July 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: Sequence alignment report (1).

Request for Continued Examination

1) A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicants' submission filed on 07/20/05 has been entered.

Status of Claims

2) Claim 23 has been canceled via the amendment filed 07/20/05.
Claims 1, 18 and 21 have been amended via the amendment filed 07/20/05.
Claims 1, 3, 4, 11-13, 18 and 21 are pending.
Claims 1, 3, 4, 11, 18 and 21 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Withdrawn

5) The rejection of claim 18 made in paragraph 28(a) of the Office Action mailed 02/23/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

6) The rejection of claim 21 made in paragraph 28(b) of the Office Action mailed 02/23/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

7) The rejection of claim 21 made in paragraph 28(c) of the Office Action mailed 02/23/05 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants'

amendment to the claim.

8) The rejection of claim 21 made in paragraph 10 of the Office Action mailed 02/27/04 and maintained in paragraph 25 of the Office Action mailed 02/23/05 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn.

9) The rejection of claims 1, 3 and 11 made in paragraph 27 of the Office Action mailed 02/23/05 under 35 U.S.C § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendment to the base claims.

10) The rejection of claims 11, 18 and 23 made in paragraph 29 of the Office Action mailed 02/23/05 under 35 U.S.C § 102(b) as being anticipated by Choi *et al.* (WO 98/18930 A2 – already of record) ('930) as evidenced by Harlow *et al.* (*In: Antibodies: A Laboratory Manual*. Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988), is withdrawn in light of Applicants' amendment to the claims.

Rejection(s) Maintained

11) The rejection of claims 1, 3 and 11 made in paragraph 10 of the Office Action mailed 02/27/04 and maintained in paragraph 25 of the Office Action mailed 02/23/05 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is maintained for reasons set forth therein and herebelow.

Applicants submit the following arguments: (a) Applicants have amended claim 1 to recite that the immunogenic polypeptide elicits production of an antibody that binds to the polypeptide having the amino acid sequence of SEQ ID NO: 8; (b) Such limitation replaces the limitation for binding to *S. pneumoniae* and is specifically supported in the application at page 13, lines 24-30, where it is stated that 'a polypeptide of the invention, when administered to a mammal, will elicit production of an antibody that binds the native polypeptide'.

Applicants' arguments have been carefully considered, but are not persuasive. Claim 1, as amended, includes the functional limitation: the recited isolated polypeptide having an amino acid sequence 'with at least 80% identity to the amino acid sequence of SEQ ID NO: 8' (i.e., a polypeptide variant having as least 20% non-identity with SEQ ID NO: 8) wherein said polypeptide when administered to a mammal elicits 'an antibody that binds to a polypeptide

consisting of the sequence of SEQ ID NO: 8'. The polypeptide of claim 3 has at least 95% identity to SEQ ID NO: 8 and is associated with the same functional limitations. Claim 11 continues to require the polypeptide to 'elicit protective antibodies in a mammal against *S. pneumoniae*'. Lines 24-30 from page 13 of the specification are reproduced below, which do not provide enablement for the above-identified polypeptide variants of SEQ ID NO: 8 having as much as 5 to 20% non-identity thereto wherein the polypeptide variants concurrently have the recited biologic functions:

Antibodies generated against a polypeptide vaccine corresponding to a sequence of the present invention can be obtained by direct injection of the polypeptide into an animal or by administering the polypeptide to an animal, preferably a nonhuman. The antibody so obtained will then bind the polypeptide itself. In this manner, even a sequence encoding only a fragment of the polypeptide can be used to generate antibodies binding the whole native polypeptide.

This part of the specification appears to describe: (a) an antibody that binds to the homologous or corresponding polypeptide when the polypeptide is administered to an animal; and (b) the use of a polypeptide fragment (as opposed to a polypeptide variant) to generate antibodies that bind to the native polypeptide. This part of the specification however has nothing to do with a 5 to 20% non-identical polypeptide variant eliciting antibodies that bind to the native polypeptide of SEQ ID NO: 8 and that protect a mammal against *S. pneumoniae*. The rejection stands.

12) The rejection of claim 11 made in paragraph 11 of the Office Action mailed 02/27/04 maintained in paragraph 26 of the Office Action mailed 02/23/05 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is maintained for reasons set forth therein.

Applicants have deleted the dependency of claim 11 from claim 23, but have advanced no specific arguments with regard to this rejection. With regard to the dependency of claim 11 from claim 4, there is no lack of enablement. However, with regard to the dependency of claim 11 from claim 1 or 3, the rejection stands. The precise structure of a polypeptide variant of the amino acid sequence of SEQ ID NO: 8 having 5 to 20% non-identity with the amino acid sequence of SEQ ID NO: 8 that has the capacity to elicit 'protective antibodies in a mammal against *Streptococcus pneumoniae*' is not described. Such a variant having the recited function is not enabled in the instant case. As set forth in paragraph 26 of the Office Action mailed

02/23/05, absent a showing, the 'protective' capacity of a given polypeptide variant is not predictable. The rejection stands.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

13) Claims 1, 3 and 11 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1, as amended, includes the new limitations: an isolated polypeptide having an amino acid sequence with at least 80% identity to the amino acid sequence of SEQ ID NO: 8 wherein said polypeptide when administered to a mammal elicits an antibody 'that binds to a polypeptide consisting of the sequence of SEQ ID NO: 8'. Applicants state that lines 24-30 on page 13 of the specification provide the descriptive support for the added limitations. However, there is no descriptive support in these parts of the specification, as originally filed, for an immunogenic composition comprising an isolated polypeptide having an amino acid sequence with 'at least 80%' or 'at least 95%' identity to the amino acid sequence of SEQ ID NO: 8 wherein the polypeptide when administered to a mammal elicits an antibody 'that binds to a polypeptide consisting of the sequence of SEQ ID NO: 8'. An isolated polypeptide having 'at least 80%' or 'at least 95%' identity to the amino acid sequence of SEQ ID NO: 8 and concurrently having the ability to elicit an antibody 'that binds to a polypeptide consisting of the sequence of SEQ ID NO: 8', or the ability to 'elicit protective antibodies in a mammal against *S. pneumoniae*' lacks descriptive support in the specification, as originally filed. Therefore, the above-identified limitations in the claim(s) are considered to be new matter. New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). See M.P.E.P. 608.04 to 608.04(c).

Applicants are invited to point to the descriptive support in specific part(s) of the disclosure, as originally filed, for the limitations identified above, or to remove the new matter from the claims and/or the base claim(s).

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

14) Claim 21 is rejected under 35 U.S.C. § 112, first paragraph, because the specification while being enabling for an immunogenic composition comprising immunogenic fragments selected from those consisting of amino acid residues 650-773, 640-773, 630-773, 610-773 and 600-773 of the amino acid sequence of SEQ ID NO: 8, does not reasonably provide enablement for a 'vaccine' comprising immunogenic fragments selected from residues 650-773, 640-773, 630-773, 610-773 and 600-773 of the amino acid sequence of SEQ ID NO: 8, as recited currently.

Instant claim is evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

The instantly claimed product is a 'vaccine' comprising the recited immunogenic fragments of a *S. pneumoniae* polypeptide having the amino acid sequence of SEQ ID NO: 8. A 'vaccine must by definition trigger an immunoprotective response in the host vaccinated; mere antigenic response is not enough'. *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The instant application on page 12, lines 14-26 describes specific immunogenic fragments of SEQ ID NO: 8, i.e., fragments consisting of amino acid residues 657-773, 650-773, 630-773, 610-773 and 600-773 of the amino acid sequence of SEQ ID NO: 8. Only one of these immunogenic fragments, i.e., the one consisting of amino acid residues 657-773 of SEQ ID NO: 8, is described as providing a moderate protection of about 40% in mice against a challenge with *S. pneumoniae*. None of the rest of the immunogenic fragments recited therein were evaluated for protection against *S. pneumoniae* infection either by an *in vivo* protection assay in an accepted animal model, or by one or more *in vitro* assays correlative of protection in human or non-human animals. In other words, the existence

of one or more protective epitopes in these immunogenic fragments has not been shown. While the recited fragments are expected in the art to be immunogenic, their ability to 'protect' and serve as a 'vaccine' is not predictable absent a concrete showing, which in the instant application is lacking. Predictability or unpredictability is one of the *Wands* important factors for enablement. Although the recited fragments are expected to elicit antibodies to the respective fragments, their ability to specifically recognize the native polypeptide and/or provide 'protection' against *Streptococcus pneumoniae* cannot be predicted since protection is immunospecific to an antigen. There is lack of showing that the claimed immunogenic fragments remain *Streptococcus pneumoniae*-specific and confer protection against *Streptococcus pneumoniae*. With regard to protective ability, the enablement or a concrete showing in the instant case is limited to the full length polypeptide having the amino acid sequence of SEQ ID NO: 8, and an immunogenic fragment consisting of amino acid residues 657-773 of SEQ ID NO: 8. Therefore, due to the lack of specific guidance and disclosure as to the ability of the recited polypeptide fragments to serve as a 'vaccine'; the lack of demonstration of their protective ability in an *in vivo* animal model or by an *in vitro* assay correlative of protection; the lack of working examples enabling the full scope of the claims; the art-recognized unpredictability factor associated with the functions of polypeptide fragments; the breadth of the claims; and the quantity of experimentation necessary, undue experimentation would have been required to practice the invention as claimed. The claim is viewed as not meeting the scope of enablement provision of 35 U.S.C. § 112, first paragraph.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

15) Claims 1, 3, 11 and 21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1, as amended, is vague and indefinite in the recitation: 'polypeptide consisting of the sequence'. For the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the limitation with --polypeptide consisting of the amino sequence--.

(b) Claim 21, as amended, is vague and indefinite in the recitation: 'selected from residues'. For the purpose of distinctly claiming the subject matter, it is suggested that

Applicants replace the limitation with -- selected from amino acid residues--.

(c) Claims 3 and 11, which depend from claim 1, are also rejected as being indefinite, because of the indefiniteness identified above in the base claim.

Objection(s)

16) In line 2 of claim 1, the comma following the limitation 'polypeptide' is unnecessary and should be deleted.

Relevant Art

17) The art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicant's disclosure:

- Le Page *et al.* (US 2003/0134407 A) and its provisional application cited therein, 60/125,329 filed 3/19/1999, disclose a polypeptide having an amino acid sequence that is 100% identical to the instantly recited SEQ ID NO: 8. See the attached sequence alignment report. US 2003/0134407 A is a publication of the application 09/769,744, which is a continuation of the PCT application PCT/GB99/02452, filed before 29 November 2000.

Remarks

18) Claims 1, 3, 11 and 21 stand rejected. The subject matter of claim 4 and 18 are free of prior art currently of record.

19) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of amendments, responses or papers is (571) 273-8300.

20) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.Mov>. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

21) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

September, 2005


S. DEVI, PH.D.
PRIMARY EXAMINER

```

Matches 773; Conservative 0; Mismatches 0; Indels 0; Gaps 0;
QY 1 KLGELAESKPTNLANQKESGLAKDTTOVERHHQENESSINKESPTIDNISTIRDPENK 60
DB 1313 KLGELAESKPTNLANQKESGLAKDTTOVERHHQENESSINKESPTIDNISTIRDPENK 1372
QY 61 DLKLLIKKCPREVDPTSETGKMEHYDYKYDKNGIAYDDGTDLYETECLEIKSKI 120
DB 1373 DLKLLIKKCPREVDPTSETGKMEHYDYKYDKNGIAYDDGTDLYETECLEIKSKI 1432
QY 121 YGVLSPKSGHGFBIIGKI SNVSRNAKYTYGNNTSISIKATKTDPSKNTMTDLYANIND 180
DB 1433 YGVLSPKSGHGFBIIGKI SNVSRNAKYTYGNNTSISIKATKTDPSKNTMTDLYANIND 1492
QY 181 IVDDLAPAGDMRLFYKNDOKKABIKIRMPKCKETKSEYVYVSSYGVNVIHLEGEDLSKN 240
DB 1493 IVDDLAPAGDMRLFYKNDOKKABIKIRMPKCKETKSEYVYVSSYGVNVIHLEGEDLSKN 1552
QY 241 KPDNLITNESGKIYSDSEKQOYLLKONIILRKQYALKVTTNPGKTDMLSGHGYVSKEDI 300
DB 1553 KPDNLITNESGKIYSDSEKQOYLLKONIILRKQYALKVTTNPGKTDMLSGHGYVSKEDI 1612
QY 301 AKIQKANPNLRLALETIYADSRNVSDGRSTOSVLMSALDGFNIIRYQVTFPRMDKGEA 360
DB 1613 AKIQKANPNLRLALETIYADSRNVSDGRSTOSVLMSALDGFNIIRYQVTFPRMDKGEA 1672
QY 361 IDKGNLVTDSSKLVLFGKDDKEYTGGDKPNVBAIKEDGSMPLDTCVNLSDMKSNYFP 420
DB 1673 IDKGNLVTDSSKLVLFGKDDKEYTGGDKPNVBAIKEDGSMPLDTCVNLSDMKSNYFP 1732
QY 421 SKSNKIYVRNPFPILAGKISDKGGPNWELRVNHSVVDNTLIYCDLHIDNTDPIKLVK 480
DB 1733 SKSNKIYVRNPFPILAGKISDKGGPNWELRVNHSVVDNTLIYCDLHIDNTDPIKLVK 1792
QY 481 DGDINDWGMKDYKANGFPDKVTMDGCVYLGQYSDLAKAAGVHYQPLXNVKPEVNID 540
DB 1793 DGDINDWGMKDYKANGFPDKVTMDGCVYLGQYSDLAKAAGVHYQPLXNVKPEVNID 1852
QY 541 PKNSTISLEYADGKSVVFNINDKRNNGPDGEIOSCHYIINKEKSTSPNDIKOIIDKTLNIK 600
DB 1853 PKNSTISLEYADGKSVVFNINDKRNNGPDGEIOSCHYIINKEKSTSPNDIKOIIDKTLNIK 1912
QY 601 IVVDPFARNTTVKCPILNKDTQVSELPKPHRVTVVTIONGKMSSTIVSESDPILPVYKGE 660
DB 1913 IVVDPFARNTTVKCPILNKDTQVSELPKPHRVTVVTIONGKMSSTIVSESDPILPVYKGE 1972
QY 661 LERKQYQDGEWISGFEKPKKADAGTVINLSKDTPIKVPFKKIEKKKEENKPTFVSKKON 720
DB 1973 LERKQYQDGEWISGFEKPKKADAGTVINLSKDTPIKVPFKKIEKKKEENKPTFVSKKON 2032
QY 721 POWNHSQLNESHUKEDLOREHESQKSDSTQVATVLDKNHSSKSTTNPNK 773
DB 2033 POWNHSQLNESHUKEDLOREHESQKSDSTQVATVLDKNHSSKSTTNPNK 2085

```

SEQ ID No. 8

```

RESULT 2
US-09-769-744A-28
; Sequence 28, Application US/09769744A
; Publication No. US20030134407A1
; GENERAL INFORMATION:
; APPLICANT: Le Page, Richard WP
; APPLICANT: Wells, Jeremy M
; APPLICANT: Hanniffy, Sean B
; APPLICANT: Hanebro, Philip M
; TITLE OF INVENTION: Proteins
; FILE REFERENCE: PRC/P21122NO
; CURRENT APPLICATION NUMBER: US/09/769,744A
; PRIOR FILING DATE: 2001-01-26
; PRIOR APPLICATION NUMBER: PCT/GB99/02452
; PRIOR FILING DATE: 1999-07-27
; PRIOR APPLICATION NUMBER: GB 9816336.3
; PRIOR FILING DATE: 1998-07-27
; PRIOR APPLICATION NUMBER: US 60/125329
; PRIOR FILING DATE: 1999-03-19
; NUMBER OF SEQ ID NOS: 196
; SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 28
; LENGTH: 2119
; TYPE: PRT
; ORGANISM: Streptococcus pneumoniae
US-09-769-744A-28

```

Query Match 100.0%; Score 4026; DB 10; Length 2119;
 Best Local Similarity 100.0%; Pred. No. 5.8e-216;